Carbohydrate Malabsorption Following Acarbose Administration

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Carbohydrate absorption was assessed during acarbose administration to investigate the actions of this drug. In 7 healthy volunteers, breath hydrogen concentration was measured at 15-min intervals after administration of 6 g of lactulose, and continued until 4 h after the breath hydrogen level exceeded its pretreatment value by ≥10 ppm, then the amount of undigested carbohydrate was calculated following administration of various doses of acarbose and Ensure Liquid. Breath hydrogen data were also obtained before and after administration of acarbose to 8 patients with Type 2 diabetes mellitus for 2 and 4 months. After administration of 50 mg of acarbose with 250 ml or 500 ml of Ensure, the mean amount of unabsorbed carbohydrate was 5.3 g and 7.7 g, respectively, while unabsorbed carbohydrate increased to 10.8 g after 100 mg of acarbose with 500 ml of Ensure. In the diabetic patients, breath hydrogen excretion decreased to 31.6 % of baseline after 2 months of acarbose administration, indicating decreased carbohydrate malabsorption. Despite this, the haemoglobin A_{1c} level remained stable after 5 months. In conclusion, the extent of carbohydrate malabsorption depended on the acarbose dose and the carbohydrate load. Although carbohydrate malabsorption decreased with continued acarbose administration, the improvement of glycaemic control was maintained. © 1998 John Wiley & Sons, Ltd.

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Introduction

Acarbose is an α-glucosidase inhibitor that blocks the activity of the glucosidases, α-amylase, α-maltase, and α-sucrase.[1–3] It inhibits the increase of postprandial blood glucose in diabetic patients when administered with food.[4,5] However, it also causes gastrointestinal side-effects such as abdominal fullness and increased flatulence. Such symptoms are common in the initial stages of therapy, although they tend to decrease with continued administration.[6] The gastrointestinal symptoms result from the degradation of unabsorbed carbohydrate by intestinal bacteria and subsequent production of hydrogen and carbon dioxide.[7] Some of the hydrogen gas is excreted in expired air.[8–10] Acarbose administration also causes hydrogen gas to be excreted in expired air,[7–11] but it is not clear how much unabsorbed carbohydrate reaches the large intestine after a dose of the drug or what effect long-term acarbose administration has on carbohydrate absorption.

The development of tolerance to the gastrointestinal symptoms caused by acarbose suggests that carbohydrate malabsorption may decrease during long-term therapy. The present study was conducted to investigate the acute effect of acarbose administration on carbohydrate absorption in healthy volunteers and the chronic effect over 4 months in patients with Type 2 diabetes mellitus.

Subjects and Methods

Subjects

Seven healthy adult volunteers (6 men and 1 woman, aged 21–34 years) were recruited for the acute study. None of the subjects was receiving medication or had a history of gastrointestinal or respiratory disease and no abnormalities were detected by general laboratory screening tests conducted prior to the study.

Eight patients with Type 2 diabetes mellitus, with inadequate glycaemic control on diet alone were enrolled in the chronic study (6 men and 2 women, aged 46–68 years). These patients had been hospitalized either to achieve stable blood glucose control or for education and had shown an inadequate response after at least 2

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weeks of dietary therapy. The criteria for enrolment were a fasting plasma glucose >7.8 mmol l^{-1} or a postprandial plasma glucose >11.1 mmol l^{-1}. None of the patients had received insulin or sulphonylureas.

Each subject gave informed consent to the study, which was performed in accordance with the principles of the Helsinki Declaration.

Acute Effect of Acarbose on Carbohydrate Absorption

Lactulose is a disaccharide which does not undergo glycolysis in the human small intestine and therefore very little of it is absorbed.[12] Hydrogen produced by intestinal fermentation is excreted in expired air when lactulose is administered to humans. Therefore, it is possible to estimate the amount of unabsorbed carbohydrate by measuring expired hydrogen after feeding and comparing it against the results with lactulose as the standard.[13]

After an overnight fast, subjects were given 6 g of lactulose with a test meal (250 ml of Ensure Liquid®: Dinabot Co. Ltd, Tokyo, Japan) to confirm that breath hydrogen increased by 10 ppm or more compared to the pretreatment value. Next, they were given 500 ml of Ensure Liquid alone and breath hydrogen was monitored for at least 6 h to confirm that the concentration did not increase. Finally, acarbose (Glucobay®: Bayer Yakuhin, Ltd, Osaka, Japan) and Ensure were administered together. First, the subject took acarbose with water and then consumed Ensure over approximately 10 min. Subjects were given either (a) 50 mg of acarbose with 250 ml of Ensure, (b) 50 mg of acarbose with 500 ml of Ensure, or (c) 100 mg of acarbose with 500 ml of Ensure in random order. Breath hydrogen was determined before dosing and at 15-min intervals after administration. Monitoring was continued for 4 h from the time when an increase of ≥ 10 ppm relative to the pretreatment baseline was observed (the orocaecal transit time). If breath hydrogen concentration did not increase within 6 h, the test was terminated. There was a washout interval of at least 1 week between each test and all tests were completed within a 2-month period. The composition of Ensure Liquid was as follows: 250 ml contained 250 kcal of energy comprising 34.3 g of carbohydrate (24.5 g of dextrin and 9.8 g of sucrose), 8.8 g of fat, and 8.8 g of protein.[14]

The amount of unabsorbed carbohydrate was calculated in accordance with the method of Rumessen *et al*.[13] The baseline breath hydrogen concentration was designed as Cb, while the area under the breath hydrogen concentration–time curve for 4 h after it had increased by ≥ 10 ppm relative to the baseline (AUC) was determined from the following formula:

$$\mathrm{AUC} = \{(C_0+C_{15})\times 15/2+(C_{15}+C_{30})\times 15/2 +\ldots+(C_{225}+C_{240})\times 15/2\}/60\text{-Cb}\times 4(\mathrm{ppm}\times \mathrm{h})$$

where Cn is the breath hydrogen concentration at *n* min after the orocaecal transit time.

The AUC was calculated for each test and the amount of unabsorbed carbohydrate was obtained from the following formula:

$$\text{Unabsorbed carbohydrate (g)} = 6\text{ g} \times \text{AUC (acarbose + ensure)/AUC (lactulose)}$$

All gastrointestinal symptoms occurring during the test were recorded, with the severity and the time of onset being noted. The severity was classified as: none; mild for symptoms that were not uncomfortable; moderate for symptoms that were uncomfortable but not painful; severe for symptoms that were accompanied by pain.

Chronic Effect of Acarbose on Breath Hydrogen

Initially, each patient was given 100 mg of acarbose with 500 ml of Ensure and the breath hydrogen concentration was determined at 1-h intervals from before loading until 9 h afterwards. The AUC was calculated from the time breath hydrogen increased by ≥ 10 ppm over the pretreatment level until the end of testing. Then the patients were started on acarbose at a dose of 50 mg three times daily. The dose was increased to 100 mg three times daily in some patients, depending on their abdominal symptoms and clinical response. The loading test (100 mg of acarbose with 500 ml of Ensure) was repeated on an outpatient basis after 2 and 4 months of acarbose administration, breath hydrogen excretion was determined, and the AUC was calculated as in the initial test. The haemoglobin A_{1C} (HbA_{1c}) level was measured at monthly intervals from before the start of acarbose administration until after 5 months of treatment.

Expired air was sampled using a collection bag with a scissor valve (GaSampler®, Quintron Instruments, Milwaukee, Wisconsin, USA). Hydrogen gas concentrations were determined by gas chromatography using a MicroLyzer Model 12i® (Quintron Instruments, Milwaukee, Wisconsin, USA).[15] HbA_{1c} was measured by high performance liquid chromatography.

Results are expressed as the mean ± SD. Differences were tested for significance using Student's paired *t*-test (two-tailed) and a p value <0.05 was considered significant.

Results

Acute Effect of Acarbose on Carbohydrate Absorption

Increased breath hydrogen concentrations were observed in all 7 healthy volunteers following lactulose administration, while no increase was noted after 500 ml of Ensure alone. The AUC following lactulose loading was 106.8 ± 24.3 ppm h^{-1}. The baseline breath hydrogen

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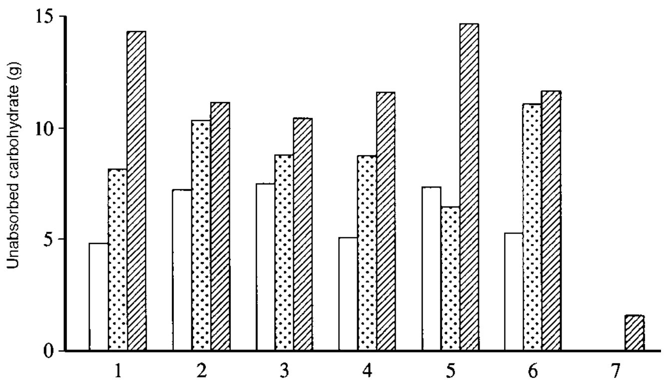

Figure 1. Amount of unabsorbed carbohydrate in the 7 healthy subjects. Administration of 50 mg of acarbose with 250 ml of Ensure (open columns), 50 mg of acarbose with 500 ml of Ensure (dotted columns), and 100 mg of acarbose with 500 ml of Ensure (hatched columns)

Table 2. Abdominal symptoms after administration of acarbose with Ensure in the healthy subjects

Subjects			Acarbose + Ensure		
No.	Age	Sex	50 mg + 250 ml	50 mg + 500 ml	100 mg + 500 ml
1	24	M	–	–	F(+)
2	34	M	–	F(+)	F(+)
3	32	M	–	F(+)	–
4	21	F	–	–	F(++), LS(++)
5	25	M	–	–	–
6	34	M	–	F(+), LS(+)	F(+), LS(+)
7	31	M	–	–	–

F flatulence; LS loose stools; (+) mild; (++) moderate; (+++) severe.

concentration was 7.4 ± 6.1 ppm in the lactulose loading test and was 4.5 ± 4.0, 5.4 ± 4.0, and 5.3 ± 4.4 ppm, respectively, following administration of 50, 50, and 100 mg of acarbose with 250, 500, and 500 ml of Ensure. There were no significant differences between these different doses.

The amount of unabsorbed carbohydrate determined from the AUC is shown in Figure 1 and is expressed as a percentage of the carbohydrate in the test meal in Table 1. When 50 mg of acarbose was given with 250 ml of Ensure, 5.3 ± 2.6 g of carbohydrate remained unabsorbed. After 50 mg of acarbose was given with 500 ml of Ensure, the unabsorbed carbohydrate level was significantly higher than that obtained with 250 ml of Ensure ($p<0.05$); after 100 mg of acarbose was given with 500 ml of Ensure, unabsorbed carbohydrate levels were significantly higher than in the other tests ($p<0.01$ and $p<0.05$, respectively). Unabsorbed carbohydrate increased when 500 ml of Ensure was administered compared to 250 ml in 6 of the 7 healthy subjects. The exception was case number 7, who showed no signs of carbohydrate malabsorption at any dose of acarbose, because these was no increase of the breath hydrogen concentration.

The gastrointestinal symptoms noted during the study are shown in Table 2. The symptoms included increased passage of flatus, abdominal discomfort, borborygmi, and loose stools, but none of the subjects experienced abdominal pain or watery diarrhoea. The first three symptoms, presumably due to an increase of gas in the bowel, were collectively labelled as 'flatulence.' No gastrointestinal symptoms occurred following administration of 50 mg of acarbose with 250 ml of Ensure. When 50 mg of acarbose was given with 500 ml of Ensure, however, flatulence occurred in 3 out of 7 subjects and loose stools in 1. After 100 mg of acarbose was given with 500 ml of Ensure, flatulence occurred in 4 subjects and loose stools in 2. These symptoms were all mild to moderate. Flatulence appeared as the breath hydrogen concentration was starting to rise, while loose stools were noted near the conclusion of the test.

Chronic Effect on Breath Hydrogen

In all 8 diabetic patients, breath hydrogen levels increased by ≥10 ppm after the initial loading test, with an AUC of 178.0 ± 72.5 ppm h^{-1} (Figure 2). Acarbose was started at a dose of 50 mg three times daily. In 3 patients with few abdominal symptoms, the dose was increased to 100 mg three times daily within 2 months. After 2 months, the breath hydrogen AUC was significantly decreased to 54.8 ± 56.5 ppm h^{-1} (31.6 % of the value in the initial loading test, $p<0.001$), and no increase of hydrogen was detected in 3 subjects. After 4 months of acarbose treatment, the breath hydrogen AUC was decreased further to 33.3 ± 49.0 ppm h^{-1} and no increase of hydrogen was observed in 4 patients.

At the start of acarbose administration, HbA_{1C} was 8.4 ± 0.9 %. After 1 month of treatment, there was a significant decrease to 7.7 ± 0.6 % and there was further

Table 1. Mean amount of unabsorbed carbohydrate in the healthy subjects

Test	Unabsorbed carbohydrate (g)	% Total carbohydrate	% Total calories
50 mg of acarbose + 250 ml of Ensure	5.3 ± 2.6 }a } b	15.5 ± 7.6	8.5 ± 4.2
50 mg of acarbose + 500 ml of Ensure	7.7 ± 3.7 }a	11.2 ± 5.4 }a	6.2 ± 3.0 }a
100 mg of acarbose + 500 ml of Ensure	10.8 ± 4.2 } b	15.7 ± 6.1	8.6 ± 3.3

Values are mean ± SD.
[a]$p<0.05$, [b]$p<0.01$.

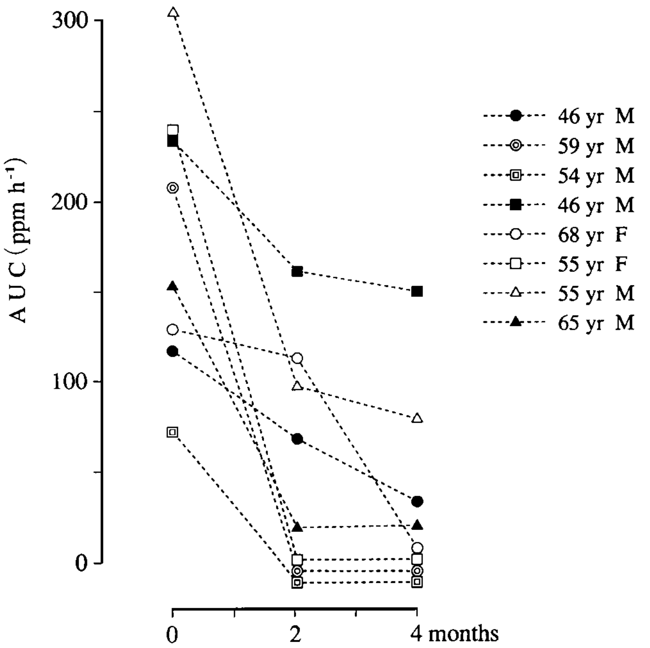

Figure 2. Area under the H_2 excretion curve (AUC) in the diabetic patients. The AUC was measured from the orocaecal transit time to 9 h after administration of 100 mg of acarbose with 500 ml of Ensure. All patients were treated with 150 or 300 mg of acarbose daily for 4 months, and the AUC was measured at 0, 2, and 4 months after the start of treatment

reduction to 7.3 ± 0.8 % at 2 months. Similar levels were maintained up to 5 months (7.4 ± 0.8 %).

Discussion

In this study, the effect of acarbose on carbohydrate malabsorption was investigated. The main finding was that carbohydrate malabsorption occurred after acute dosing in healthy subjects but decreased during prolonged treatment of people with Type 2 diabetes mellitus, although their improvement in glycaemic control remained stable.

Since hydrogen gas was excreted in expired air following acarbose administration, this drug not only delays the digestion of polysaccharides but also permits carbohydrates to pass unabsorbed through the digestive tract. Very few studies have investigated how much carbohydrate remains unabsorbed and it is unclear what effect this may have on nutrition. Caspary *et al.* administered 100 g of sucrose with 200 mg of acarbose and reported that the increase in breath hydrogen concentration (AUC) was twice that achieved by 20 g of lactulose.[7] Jenkins *et al.* showed that approximately 20 % of 50 g of sucrose was not absorbed when given with 50 mg of acarbose, while a 200 mg dose of the drug almost completely inhibited sucrose absorption.[11] To investigate carbohydrate malabsorption after a meal during acarbose administration, we used Ensure. A solid test meal might have been preferable but it is difficult to maintain a uniform nutritional composition of solid food. The composition of Ensure is similar to the recommended diet for diabetic patients, except that it is liquid.[16]

There have been major variations between previous studies in the method of calculating carbohydrate malabsorption by comparing the breath hydrogen AUC obtained after a reference dose of lactulose.[17–19] To calculate the total AUC requires more than 10 h of data collection. However, Rumessen *et al.* showed that AUC for 4 h was closely correlated with the total AUC,[13] so we calculated the amount of unabsorbed carbohydrate based on AUC for 4 h in accordance with the method of Rumessen.

On the basis of data obtained after administering 500 ml of Ensure (500 kcal) with 50 or 100 mg of acarbose, it appears that 11.2–15.7 % of the carbohydrate load, equivalent to 6.2–8.6 % of the total calorie intake may be unabsorbed during acarbose therapy. Severe carbohydrate malabsorption generally leads to watery diarrhoea and weight loss.[20] We observed an increase of flatulence and loose stools in our acute study and these symptoms became more severe as the amount of unabsorbed carbohydrate increased. However, there was no watery diarrhoea. Moreover, there have been no reports of marked weight loss during acarbose administration. Unabsorbed carbohydrates reaching the colon are converted to short chain fatty acids and then are partly absorbed,[21,22] so the real calorie loss is probably less than that calculated. Accordingly, the degree of carbohydrate malabsorption caused by acarbose may have little effect on overall nutritional status. However, it may be wise to use caution when treating diabetic patients who are in a poor nutritional state.

In the present study, we compared the amount of unabsorbed carbohydrate following administration of three different combinations of acarbose and Ensure. Our data show that acarbose-induced inhibition of carbohydrate absorption is greater at higher drug dosages and with higher carbohydrate load. Patients with severe gastrointestinal symptoms possibly have an excessive food intake during acarbose therapy. Thus, food intake as well as drug dose should be reviewed in patients with abdominal symptoms during acarbose therapy, and dietary adjustments may help.

The abdominal symptoms caused by acarbose have been reported to decrease gradually with continued administration,[6,23] but the mechanism underlying this effect is unclear. We investigated the changes of the breath hydrogen excretion profile over time in 8 diabetic patients. It is difficult to estimate long-term changes in the actual amount of unabsorbed carbohydrate, because the standard lactulose loading test is not useful for this purpose.[13] Therefore, we used breath hydrogen excretion in this study and found that it clearly decreased as acarbose administration was continued in every patient. This was probably caused by a decrease of carbohydrate malabsorption. Breath hydrogen excretion is also affected by the intestinal bacterial flora and obligate anaerobes are reported to increase in the intestines following acarbose administration.[24] However, such a change

should not reduce hydrogen gas production, so the decrease of breath hydrogen excretion that we detected can be attributed to a decrease in the degree of carbohydrate malabsorption, perhaps following adaptation of the intestinal digestive enzymes to continued acarbose therapy.

Judging from the HbA_{1c} profile, the improvement of glycaemic control was maintained even after a decrease of carbohydrate malabsorption. The effect of acarbose on glucose metabolism is mainly related to a decrease of the early postprandial plasma glucose peak. The persistence of a beneficial effect on HbA_{1c} suggests that delayed carbohydrate absorption in the proximal small intestine was adequately maintained over the long term despite the decreased overall inhibition of carbohydrate absorption. Therefore, the decrease of unabsorbed carbohydrate was possibly due to improved carbohydrate absorption in the distal small intestine secondary to an increase in the activity of α-glucosidases.

In conclusion, we found that the extent of carbohydrate malabsorption depends on both the acarbose dose and the carbohydrate load. Although the amount of unabsorbed carbohydrate decreased gradually with continued acarbose administration, the beneficial effect on glycaemic control was maintained.

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References

1. Schmidt DD, Frommer W, Junge B, Müller L, Wingender W, Truscheit E. α-Glucosidase inhibitors. New complex oligosaccharides of microbial origin. *Naturwissenschaften* 1977; **64**: 535–536.
2. Caspary WF, Graf S. Inhibition of human intestinal α-glucosidehydrolases by a new complex oligosaccharide. *Res Exp Med (Berl)* 1979; **175**: 1–6.
3. Suehiro I, Otsuki M, Yamasaki T, Ohki A, Sakamoto C, Yuu H, *et al*. Effect of α-glucosidase inhibitor on human pancreatic and salivary α-amylase. *Clin Chem Acta* 1981; **117**: 145–152.
4. Puls W, Keup U, Krause HP, Thomas G, Hoffmeister F. Glucosidase inhibition: a new approach to the treatment of diabetes, obesity, and hyperlipoproteinaemia. *Naturwissenschaften* 1977; **64**: 536–537.
5. Hayakawa T, Noda A, Kondo T, Okumura N. Effects of acarbose, an α-glucosidase inhibitor (BAY g 5421), on orally loaded glucose, maltose and sucrose and on blood glucose control in non-insulin dependent diabetics. *Nagoya J Med Sci* 1984; **47**: 35–41.
6. Baron AD, Eckel RH, Schmeiser L, Kolterman OG. The effect of short-term α-glucosidase inhibition on carbohydrate and lipid metabolism in type II (noninsulin-dependent) diabetics. *Metabolism* 1987; **36**: 409–415.
7. Caspary WF. Sucrose malabsorption in man after ingestion of α-glucosidehydrolase inhibitor. *Lancet* 1978; **1**: 1231–1233.
8. Calloway DH. Respiratory hydrogen and methane as affected by consumption of gas-forming foods. *Gastroenterology* 1966; **51**: 383–389.
9. Levitt MD. Production and excretion of hydrogen gas in man. *N Engl J Med* 1969; **281**: 122–127.
10. Levitt MD, Donaldson RM. Use of respiratory hydrogen (H_2) excretion to detect carbohydrate malabsorption. *J Lab Clin Med 1970;* **75**: 937–945.
11. Jenkins DJA, Taylor RH, Goff DV, Fielden H, Misiewicz JJ, Sarson DL, *et al*. Scope and specificity of acarbose in slowing carbohydrate absorption in man. *Diabetes* 1981; **30**: 951–954.
12. Carulli N, Salvioli GF, Manenti F. Absorption of lactulose in man. *Digestion* 1972; **6**: 139–145.
13. Rumessen JJ, Hamberg O, Gudmand-Høyer E. Interval sampling of end-expiratory hydrogen (H_2) concentrations to quantify carbohydrate malabsorption by means of lactulose standards. *Gut* 1990; **31**: 37–42.
14. Peters AL, Davidson MB. Effects of various enteral feeding products on postprandial blood glucose response in patients with type I diabetes. *J Parent Enteral Natr* 1992; **16**: 69–74.
15. Kondo T, Liu F, Toda Y. Milk is a useful test meal for measurement of small bowel transit time. *J Gastroenterol* 1994; **29**: 715–720.
16. American Diabetes Association. Nutritional recommendations and principles for individuals with diabetes mellitus: 1986. *Diabetes Care* 1987; **10**: 126–132.
17. Hyams JS. Sorbitol intolerance: an unappreciated cause of functional gastrointestinal complaints. *Gastroenterology* 1983; **84**: 30–33.
18. Kolars JC, Levitt MD, Aouji M, Savaiano DA. Yogurt—an autodigesting source of lactose. *N Engl J Med* 1984; **310**: 1–3.
19. Levitt MD, Hirsh P, Fetzer CA, Sheahan M, Levine AS. H_2 excretion after ingestion of complex carbohydrates. *Gastroenterology* 1987; **92**: 383–389.
20. Christopher NL, Bayless TM. Role of the small bowel and colon in lactose-induced diarrhea. *Gastroenterology* 1971; **60**: 845–852.
21. Cummings JH. Quantitating short chain fatty acid production in humans. In: Binder HJ, Cummings J, Soergel K, eds. *Short Chain Fatty Acids*. Dordrecht: Kluwer Academic Publishers, 1994: 11–19.
22. Wisker E, Feldheim W. Energy value of fermentation. In: Binder HJ, Cummings J, Soergel K, eds. *Short Chain Fatty Acids*. Dordrecht: Kluwer Academic Publishers, 1994: 20–28.
23. Sakamoto N, Shibata M, Hotta N, Kakuta H, Tomita A, Tsuchida I, *et al*. Clinical study on BAY g 5421 (acarbose) for non-insulin-dependent diabetes mellitus. *Jpn Pharmacol Ther* 1989; **17**: 633–649.
24. Maruhama Y, Nagasaki A, Kanazawa Y, Hirakawa H, Goto Y, Hishiyama H, *et al.* Effect of a glucoside-hydrolase inhibitor (BAY g 5421) on serum lipids, lipoproteins and bile acids, fecal fat and bacterial flora, and intestinal gas production in hyperlipidemic patients. *Tohoku J Exp Med* 1980; **132**: 453–462.